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LETTERS AND CORRESPONDENCE

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Acquired Dysfibrinogenemia Following Allogeneic Bone Marrow Transplantation

To the Editor: Acquired dysfibrinogenemia has been reported mainly in patients with liver diseases [1,2]. Although some coagulation abnormalities have been reported [3], an acquired dysfibrinogenemia has not been described previously in patients who underwent stem cell transplantation. We report a patient who developed a transient dysfibrinogenemia after a second allogeneic BMT.

A 21-year-old woman with ALL in second relapse underwent allogeneic BMT from her HLA-identical brother. Although a complete remission was achieved, a bone marrow relapse was diagnosed on day+227 and she underwent a second allogenic BMT from the same donor. Prior to the second transplant, she had no evidence of liver diseases, and no abnormalities were found in coagulation parameters. She was conditioned with busulfan and cyclophosphamide. Initially, a posttransplant immunosuppression was not attempted. Grade II cutaneous and intestinal GVHD developed on day+25. She was then treated with corticosteroid and cyclosporine A. On day+69, plasma fibrinogen level measured by thrombin time was 102 mg/dl and continued to decrease to 56 mg/dl on day+106. She developed macrohematuria, which was successfully treated with the transfusions of fresh frozen plasma. Fibrinogen level remained low for 7 weeks, then resolved spontaneously. The plasma fibrinogen levels on day+91 assessed by thrombin time, antigenicity, and protein clotting method were 72, 173, and 160 mg/dl, respectively. The serum fibrinogen level determined by antigenicity was 11.7 mg/dl, which was significantly higher compared with that in normal control (0.02 mg/dl). In a crossmixing test, a prolonged thrombin time was corrected by the addition of normal plasma. SDS polyacrylamide gel electrophoresis followed by immunoblotting under reducing conditions using anti-fibrinogen polyclonal antibodies showed no difference in the molecular weight of each fibrinogen chain in the patient serum compared with that in a normal control. Other coagulation parameters including APTT and PT were normal except that the serum E-fragment of fibrin- and fibrinogen-degradation product (FDP-E) was elevated (Table I).

TABLE I. Coagulation and Fibrinolysis Tests*

	Values on day + 106	Normal range
APTT	22.4 (sec)	(23–36)
PT%	78 (%)	(70–140
Fibrinogen (thrombin time)	56 (mg/dl)	(180–380)
FDP-E	484 (ng/ml)	(<100)
D-dimer	1.0 (μg/ml)	(<1.0)
PIC	0.6 (μg/ml)	(<0.8)
AT-III	106 (%)	(80–130)
Plasminogen	80 (%)	(80–120)
Factor II	124 (%)	(70–150)
Factor VII	94 (%)	(70–150)
Factor IX	148 (%)	(70–150)
Factor X	135 (%)	(70–150)
t-PA	3.6 (ng/ml)	(<10)
PAI-1	7 (ng/ml)	(<50)
t-PA-PAI complex	<6 (ng/ml)	(<10)

*AT-III, anti-thrombin III; PIC, plasmin-α2 plasmin inhibitor complex; t-PA, tissue-plasminogen activator; PAI-1, plasminogen activator inhibitor-1.

The discrepancy between fibrinogen clotting activity and its antigenicity and the result of a crossmixing test strongly suggested the presence of dysfibrinogenemia. High antigenicity of fibrinogen in serum and a high FDP-E level also support the defect in the activation process of fibrinogen. The main causes of acquired dysfibrinogenemia include liver diseases [1] and administration of cytotoxic agents [4,5]. Very mild liver dysfunction (GOT:42IU/L, GPT:60IU/L) was observed in this patient and resolved concurrently with the disappearance of dysfibrinogenemia, suggesting that it could be related to dysfibrinogenemia. No causative drugs were identified and the clinical data did not show the presence of viral infection or chronic GVHD. We should be aware of the occurrence of dysfibrinogenemia after BMT even if liver function is mildly abnormal and the replacement therapy should be initiated in the event of hemorrhage or any invasive procedures.

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Identification of a Myeloma Variant With Aggressive Biological and Clinical Characteristics: ''Early'' Plasma Cell Meningitis

To the Editor: Myelomatous meningitis [1] is a rare initial manifestation of nervous system involvement in patients with multiple myeloma (MM). This report is to our knowledge the first detailed analysis of cerebrospinal fluid (CSF) plasma cell (PC) phenotype in a case of primary meningeal myelomatosis.

A 62-year-old man was admitted at our institution for left hemiparesia. Radiographs showed punched-out lesions on the skull. Laboratory values included a hemoglobin of 145 g/liter (normal 120–150), and a white blood cell count of 21.7×10^9/liter (normal 4.0–9.0) with a differential of 92% neutrophils, 4% lymphocytes, 4% monocytes, and no circulating plasmocytes. The platelet count was 349×10^9/liter (normal 150–450). Serum creatinine was 117 μmol/liter, calcium level was 2.58 mmol/liter (normal 2.10–2.60), total protein was 73 g/liter. The β2-microglobulin was 154 nmol/liter (normal 90–210). Total immunoglobulin was 11.5 g/liter with IgG 7.5 g/liter, IgA 3.25 g/liter, and IgM 0.75 g/liter. Blood immunofixation detected a monoclonal IgAκ component without free light chains. Bone marrow examination of the iliac crest did not show abnormal PC. A lumbar puncture evidenced 600 cells/mm^3 (92% PC, 8% lymphocytes) and a monoclonal IgAκ at 1,300 mg/liter. A flow cytometry analysis of these cells was performed (Fig. 1) using the following mAbs and isotypic controls: MHC-DR class II, anti-CD2, anti-CD3, anti-CD19, anti-CD45, anti-CD38, CD56 (Immunotech, Marseille, France), anti-CD20, anti-CD40 (Pharmingen, San Diego, CA), anti-CD34 (Becton Dickinson, San Jose, CA), anti-CD22, anti-κ light chain, anti-λ light chain, anti-IgA, anti-IgG, anti-IgM (Dako, Glostrup, Denmark). All PC expressed the same IgAκ. We concluded a diagnosis of IgAκ-secreting meningeal myelomatosis. The patient received intrathecal treatment (cytarabine, methotrexate, and dexamethasone until CSF sterilization), systemic chemotherapy (cyclophosphamide 600 mg/m^2 day 1, methotrexate 8,000 mg/m^2 day 1), and a total 40 Gy of radiation on both the brain and upper cervical cord, but rapidly developed diaphragm paralysis and died from respiratory failure associated with sepsis.

The phenotypic analysis confirmed the monoclonality of PC and so excluded in particular herpes simplex meningoencephalitis, which can simulate meningeal myelomatosis [2]. The meningeal cells co-expressed PC (cyIg, CD38) and B-cell (DR, CD20, CD22, and sIg) markers, but were $CD19^-$. They showed a dispersed chromatin, scanty basophilic cytoplasm, and were of small size. This corresponded to an ''early'' PC subtype [3], which as a contributing factor to myelomatous meningitis has to be further evaluated on additional patients. A strong expression of the CD56 antigen, which is often upregulated in MM [4] and absent in extramedullary localizations [4], was detected. This molecule is involved in homotypic and heterotypic adhesive interactions with cellular and extracellular matrix components. We can suggest that $CD56^-$ bone marrow PC migrated to the CNS and then re-expressed CD56, limiting their dissemination out of the CNS. We detected on most (83%) PC a significant expression of CD40, a molecule that modulates PC clonogenicity [5]. PC could have been activated via interaction of CD40 with its ligand, CD40L, expressed on the T-lymphocytes (8% $CD2^+/CD3^+$ cells) present in the CSF.

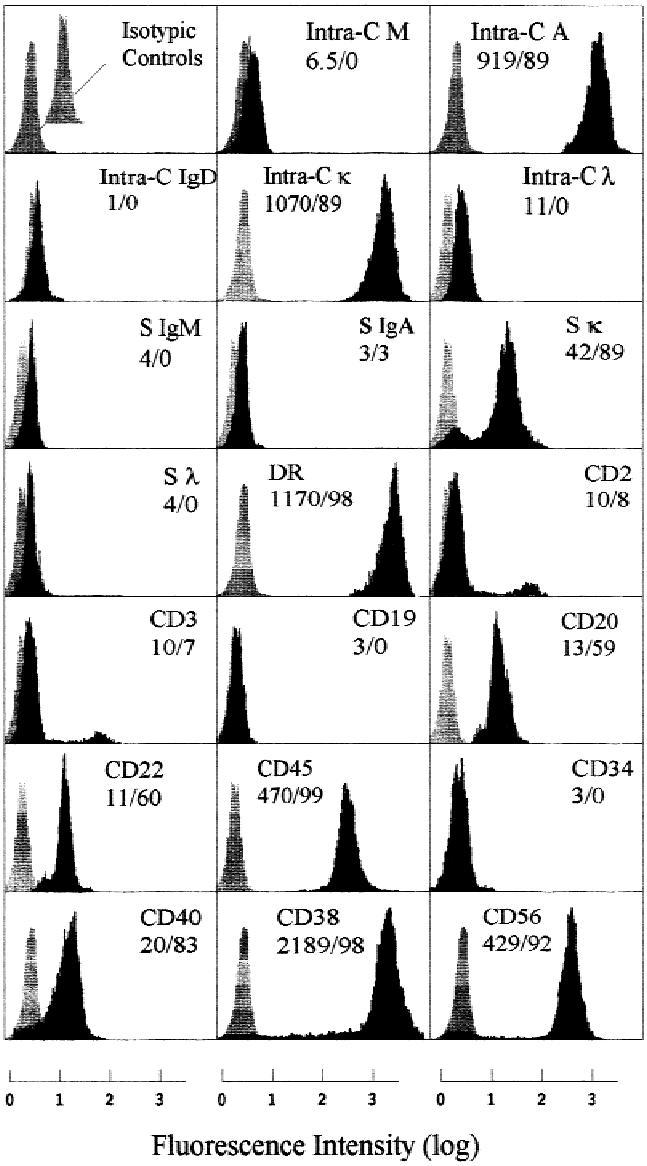

Fig. 1. Flow cytometry analysis of plasma cells in cerebrospinal fluid. For each histogram (black areas), the mean fluorescence intensity is indicated after substraction of negative control. Grey areas indicate fluorescence of isotype-matched antibody.

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Microparticles and Coronary Artery Disease

To the Editor: We read with interest the recent paper by Katopodis et al. [1] on platelet microparticles and calcium homeostasis in acute coronary ischemia. They reported that platelet microparticle levels were significantly higher in patients with unstable angina and myocardial infarction than in patient controls, and that the resting free cytoplasmic calcium, thrombin-induced Ca^{2+} influx, and release of Ca^{2+} from internal stores were all higher than in the control group. We recently demonstrated that platelet activation occurs in patients with severe coronary artery stenosis [2].

Platelet samples were obtained from 16 healthy control subjects and 65 patients, of whom 25 had angiographically normal coronary arteries and 40 had stenosis of at least one major coronary artery. In both groups of patients, CD62p expression was significantly higher than in the control group, but the difference between the two patient groups was not significant. These findings were in accordance with those of Katopodis et al. [1]. We then compared platelet microparticle levels after stratifying the patients for the number of significant coronary artery stenoses. Microparticles were detected using flow cytometry. This analysis showed that patients with three-vessel disease had significantly higher microparticle levels compared with the other subgroups.

Platelet activation is believed to play a central role in the development of coronary thrombosis and in the pathogenesis of coronary atherosclerosis. Microparticles can be detected when platelets are activated by collagen in vitro. Microparticles are also generated by high shear stress [3], such as that occurring in arteries partially occluded by atherosclerosis or spasm [4]. Ikeda et al. [5] reported that high shear stress induces Ca^{2+} influx, which may be related to the $[Ca^{2+}]i$ data of Katopodis et al. [1]. Thus, platelet microparticles may be a useful new marker for assessing the severity of coronary artery disease.

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